REMARKS

Formalities

Claims 1-27 have been canceled. Claims 28-34 have been added. Upon entry of the amendment, claims 28-34 are pending in the instant application.

The amendments to the claims do not add or constitute new matter. Support for the newly added claims may be found throughout the specification. Specifically, support for newly added claims 28-34 can be found at, for example, page 8, line 25 through page 15, line 12, page 50, lines 9-25, page 54, lines 4-15 and page 54, line 17 through page 55, line 4 of the specification. As such, no new matter has been added by this amendment.

The foregoing amendments are made solely to expedite prosecution of the instant application, and are not intended to limit the scope of the invention. Further, the cancellation of claims is made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. Applicants reserve the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

Applicants respectfully request reconsideration of the application in view of the amendments to the claims, and remarks made herein.

Objection

The Examiner's objection to claim 10 as being dependent on a non-elected claim is no longer relevant as a result of the cancellation of claims.

Rejection under 35 U.S.C. § 101

The Examiner has rejected claims 8, 10 and 14-21 under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by either a specific or substantial asserted utility or a well-established utility. Applicants respectfully traverse the rejection. Claims 8, 10 and 14-21 have been canceled. Applicants submit that the rejection as it applies to new claims 28-34 is improper in light of the arguments set forth below.

Specifically, the Examiner's rejection for lack of utility is based on an alleged lack of a correlation between the phenotypes exhibited by the claimed transgenic mice and any disease or disorder. The Examiner has further asserted that the evidence of record has failed to provide a correlation between any CASH related disease or disorder and the phenotypes exhibited by the transgenic mouse. Applicants respectfully disagree. Applicants submit that such a correlation has been provided by the instant specification, and is well-established in the art. Regardless,

Applicants do not believe that the assertion of such a correlation is necessary to establish the utility and patentability of the claimed transgenic mouse.

Claims 28-34 relate to a transgenic mouse whose genome comprises a heterozygous disruption in the CASH gene, and to methods of making and using the transgenic mouse. The instant specification has demonstrated that such a disruption in a mouse results in a phenotype specific to that mouse. In particular, the transgenic mice whose genomes comprise this disruption exhibit increased sensitivity to pain or increased susceptibility to seizure when compared to wild-type mice (See Examples 4 and 5 and Figures 3 and 4). The phenotypic parameters of the transgenic mice were evaluated in controlled studies, which are well-established in the art as tests for pain sensitivity and seizure susceptibility, and were compared to age- and gender-matched wild-type littermate mice, as is standard in the art. Applicants have asserted in the specification several uses for the transgenic knockout mouse, and such uses of transgenic knockout mice are well accepted within the art. See, for example, page 3, lines 18-25, page 4, lines 14-22, page 18, line 14 through page 19, line 12, page 19, line 18, through page 20, line 5 of the specification. The potential uses specifically relate to using the mice to discover, examine and/or develop potential treatments, which may include therapeutic agents, capable of modulating or ameliorating the phenotype exhibited by the mice, and in particular, capable of modulating or ameliorating the increased sensitivity to pain or increased susceptibility to seizure exhibited by the mice. Although Applicants have suggested these potential uses for the transgenic mice, many other well-established uses for the knockout mice would be recognized by a person skilled in the art.

It is generally accepted in the art that transgenic knockout mice, such as those described in and claimed by the instant application, represent a valuable tool for determining the function of genes in various conditions or disorders. It is also generally accepted that gene function is related to and representative of that of human, in light of the homology between the mouse and human genomes. In the present case, the transgenic mouse described in the instant specification would be accepted by the skilled artisan as a model for the role and function of the CASH gene. Applicants' disclosure related to the phenotype of the transgenic mice has established that this gene plays a role in pain and seizure susceptibility, as noted above. More particularly, loss of function of the CASH gene and/or protein has been demonstrated to have detrimental effects on pain sensitivity and seizure susceptibility in the knockout mice.

Applicants submit that in order to satisfy the utility requirements set forth in 35 U.S.C. § 101, the specification must assert a specific and substantial utility that is credible to a skilled artisan, or the utility of the claimed invention must be apparent to the skilled artisan. See MPEP § 2107. Applicants submit that the instant specification satisfies these requirements. More particularly, Applicants submit that a detectable and modifiable phenotype should be sufficient to establish the claimed transgenic mouse as useful. For example, the skilled artisan would be motivated to discover or identify agents that are capable of modulating seizure susceptibility or pain sensitivity using the claimed mouse.

Although Applicants maintain that these phenotypes are well-established as correlated or linked to disorders or diseases, specifically seizure disorders and/or pain-related disorders, the mouse would clearly be useful even without such a correlation, in that the mouse exhibits a phenotype(s) that the skilled artisan would desire to modulate or ameliorate.Applicants submit that a desire exists to ameliorate such conditions as pain or pain sensitivity, in particular abnormal/increased pain sensitivity, as well as seizure sensitivity, including abnormal or increased seizure susceptibility, seizure disorders or epilepsy. Applicants also submit that the skilled artisan would recognize that the transgenic mouse as claimed could also be used as a tool for investigating methods for preventing conditions or symptoms related to pain or seizures. As such, the claimed mice clearly have well-established, real world uses that would be evident to the skilled artisan.

The Examiner has cited Crabbe (*Science*, 1999, Vol. 284, pp 1670-1672) as establishing that results obtained from behavioral studies are greatly influenced by the genetic background of the tested mouse. However, the Crabbe reference fails to establish that phenotypic differences between a transgenic knockout mouse and a wild-type control mouse, such as those described in the instant specification, are not real and a result of the disruption of the target gene. In particular, the Crabbe reference compares only one null mutant strain (for the 5-HT1B gene) to inbred wild-type strains, and is not representative of a comparison of all mutant knockout mice and their wild-type control counterparts. Further, the number of mice tested was low, and, even according to the author, "made formal statistical assessment of reliability infeasible" (see page 1671, column 3, first full paragraph). The Crabbe reference also states that the results obtained in their study can be interpreted in different ways.

Applicants further point out that the Crabbe reference fails to describe all behavioral tests. More particularly, Crabbe fails to describe any problems related to the Hot plate test or the

Metrazol test, as used by Applicants. The Hot plate test is a well-accepted method for the evaluation of pain threshold or pain sensitivity (response to pain stimulus) and is used by many people skilled in the art to test mice, including knockout mice. The Metrazol test is used by many to evaluate the sensitivity of mice to seizures, and is considered a model for seizure susceptibility or epilepsy. Furthermore, these tests as described in the instant specification compare the heterozygous knockout mice to wild-type age- and gender-matched mice in a controlled laboratory setting. The results would be accepted by the skilled artisan as demonstrating a detectable (and useful) phenotype in the transgenic mice, and a role for the CASH gene in pain or seizure related conditions or disorders. As such, Applicants submit that the Crabbe reference fails to establish that the claimed mice lack utility, or that the phenotypes exhibited by the mice are not correlated to any conditions, disorders or diseases.

As noted above, the phenotypes of the claimed mice were determined in controlled studies and the results were compared to wild-type mice that were matched in age, gender and laboratory environment. Furthermore, the transgenic mice and wild-type mice were littermates, and as such had comparable strain backgrounds, which are commonly used in the art to create and compare knockout/transgenic mice. Therefore, the Examiner's concerns relating to strain differences in behavioral properties does not apply to the presently claimed mice.

In light of the amendments to the claims and arguments set forth above, Applicants believe the rejection of the claims under 35 U.S.C. § 101 is improper, and respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 8, 10 and 14-21 under 35 U.S.C. § 112, first paragraph, because one skilled in the art would allegedly not know how to use the claimed invention as a result of the alleged lack of either a specific or substantial asserted utility or a well-established utility for the reasons set forth in the utility rejection. Applicants respectfully traverse the rejection. Claims 8, 10 and 14-21 have been canceled. For the reasons set forth above in response to the utility rejection, Applicants submit that the rejection under 35 U.S.C. § 112, first paragraph, is improper as it relates to new claims 28-34. Therefore, Applicants respectfully request withdrawal of the rejection.

The Examiner has also asserted that the specification does not reasonably provide enablement for the transgenic mouse as claimed. The Examiner's enablement rejection relates to

the unpredictability of a phenotype in a transgenic mouse or non-human animal, and the state of the art of embryonic stem cell technology, which is limited to the mouse system, and the requirement for germline transmission of a genetic disruption resulting in the recited phenotypes. Applicants traverse each aspect of the rejection. However, the rejection has been overcome by the cancellation of claims.

Applicants have submitted new claims 28-34, which overcome the Examiner's enablement rejection. More particularly, the transgenic mouse as recited in these claims addresses each of the Examiner's concerns by: (1) reciting a transgenic mouse, (2) reciting a detectable, useful phenotype resulting from disruption of the target gene, (3) reciting germline transmission of the disruption, and/or (4) cancellation of the claim(s). Therefore, Applicants have overcome the rejection under 35 U.S.C. § 112, first paragraph, for enablement, and request withdrawal of the rejection.

It is believed that the claims are currently in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-714.

Respectfully submitted,

Date: May 3, 2004

Kelly L. Quast

Kelly L. Quast, Reg. No. 52,141

Deltagen, Inc.
1031 Bing Street
San Carlos, CA 94070
(650) 569-5100